REMARKS

Introductory Comments

Reconsideration of the above-identified application in view of the foregoing amendments and arguments is respectfully requested.

Claims 1-34 were pending. Claims 1-22 remain withdrawn from consideration. Claims 23-34 were under consideration.

Claims 23-26 have been amended to better define the invention as suggested by the Examiner. Claims 33 and 34 have been amended to better define how the slurries are made. New claims 35 and 36 have been added to include the importance of ratios as indicated below. No new matter has been added in the amendment. Support can be found in the specification at pages 3, lines 10-23, page 5, line 30 to page 8, line 2 and examples throughout the specification.

Applicants acknowledge with thanks the Examiner's consideration of Applicant's Information Disclosure Statement filed May 28, 2002.

Priority

The Examiner has denied priority benefit for claims 32-34. Instead, the Examiner has assigned the benefit date of 2/13/2002 that is the filing date of the instant non-provisional U.S. application number 10/074,782 instead of that of the provisional application 60/269,513. Specifically, the Examiner states that "the provisional application upon which priority is claimed does not disclose the claimed spray-dried preparations of either *Bacillus sphaericus* or *Bacillus thuringiensis*, or after the culture slurries of the two organisms have been mixed."

Applicants traverse the denial of priority claim from the provisional application. Information was added to the provisional application strictly by way

of illustration and examples only. Support for the claimed spray-dried preparations of either *Bacillus sphaericus* or *Bacillus thuringiensis*, or after the culture slurries of the two organisms have been mixed is found in the provisional application as follows.

Provisional application, page 3, lines 13-17; Instant application, page 3, lines 18-23:

"Additional components such as surface active agents, inert carriers, preservatives, humectants, feeding stimulants, attractants, encapsulating agents, binders, emulsifiers, dyes, U.V. protectants, buffers, drift control agents, spray deposition aids, free-flow agents or combinations thereof may also be utilized in conjunction with the combination in a larvicidal composition (Emphasis added)."

Provisional application, page 5, line 30 ; Instant application, page 6, line 6:

"The compositions disclosed above may also include additional components such as a surface active agent, an inert carrier, a preservative, a humectant, a feeding stimulant, an attractant, a drift control agent, a spray deposition aid, an encapsulating agent, a binder, an emulsifier, a dye, a U.V. protectant, a buffer, a free-flow agent, or any other component which stabilizes the active ingredient, facilitates product handling and application for the particular target pests, Diptera (Emphasis added)."

Provisional application, page 7, lines 3-4 ; Instant application, page 7, line 9:

"The formulation may also contain added drift control agents or spray deposition aids to control droplet size and to facilitate aerial application. Examples of suitable compounds for these purposes include polyvinylalcohol polymer solutions, polyamide copolymer solutions, polymerized acrylic acid derivatives and blends thereof, vegetable oils and blends thereof, petroleum oils and blends thereof, as well as natural and synthetic polymers (Emphasis added)."

Provisional application, page 10, line 24 to page 11, line 3; Instant application, page 11, lines 1-13:

"Typically, the spray-dried technical concentrate of each strain is first incorporated into a known amount of vegetable oil binder. The amount of vegetable oil binder in the formula will depend upon the amount of *B.t.i.* or *B.s.* spray technical concentrate in the formula. The typical range may vary between 1% to 15% wt/wt. depending upon the amount of *B.t.i.* or *B.s.* spray dried technical concentrate, and the type, size and absorptive property of granular carrier utilized in the formula. In this example, corn cob granules of the size classification 10/14 Mesh were used. However, other size ranges such as 5/8 Mesh, 10/20 Mesh, 10/40 Mesh are also suitable. The slurry mixture was sprayed onto the granular carrier while mixing in a suitable blender and further blended until homogenous product was obtained (Emphasis added)."

Provisional application, page 12, lines 15-21; Instant application, page 12, line 18 to page 13, line 1:

"The larvicidal combination product may also be formulated by combining the required levels of both *B.t.i.* and *B.s.* technical powders in the same binder liquid, and then impregnating or spraying onto the granular carrier such as corn cob or any other suitable carriers.

To prepare the formulation, both spray dried technical concentrates can be slurried in vegetable oil binder liquid and sprayed onto granular carrier in a suitable blender and mixed until a homogenous product is obtained. The theoretical components of the combination formulation containing *B.t.i.* at 100 ITU/mg and B.s. at 25 *B.s.* ITU/mg are provided in Table 3 below (Emphasis added)."

Provisional application, page 13, table 3; Instant application page 13, table 3:

Table 3

Component	% wt/wt	kg/Batch	Purpose
B.t.i. spray-dried technical concentrate or powder (5000 ITU/mg)	2.00	20.00	Active Ingredient
B.s. spray dried technical concentrate or powder (1000 *B.s.* ITU/mg)	2.50	25.00	Active Ingredient
Vegetable oil binder	10.00	100.00	Binder
Granular carrier	85.5	855.00	Carrier

Emphasis added.

Provisional application, page 13, lines 14-21; Instant application page 13, lines 7-15:

"The combined formulation may also be formed by pre-mixing fermentation beers or slurry concentrates of *Bti* and *Bs* at the desired solids or potency level and spray drying the slurry mixture to produce a combined technical spray dried powder concentrate. In such a formulation, the slurry concentrate may contain preservatives, stabilizers, surfactants, dispersants and other binders. The spray-dried technical concentrate or powder may then be utilized in formulating a granular product as in Examples 2 and 3 or as wettable powders, water dispersible granules, and aqueous or non-aqueous concentrates (Emphasis added)."

Thus as seen above, support for claims 32-34 from the provisional application is clear. Applicants respectfully request the Examiner to assign the benefit date from the provisional application for claims 32-34.

Rejection of Claims 23-34 Under 35 U.S.C. § 101

Claims 23-34 are rejected under 35 U.S.C. § 101 as being drawn to nonstatutory subject matter. Specifically, the Examiner asserted that as written, the claims are drawn to a biological material *per se*, which is a product of nature. Applicants have amended the claims to recite "an isolated, biologically pure strain of *Bacillus thuringeniensis*" and "an isolated, biologically pure strain of *Bacillus sphaericus*," as suggested by the Examiner in order to overcome the § 101 rejection. Applicants thank the Examiner for the suggestion and withdrawal of the § 101 rejection is requested.

Rejection of Claim 23-34 under 35 U.S.C. § 112, First Paragraph

Claims 23-34 are rejected under 35 U.S.C. § 112, First Paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the Examiner states that the bacterial strains which are essential to the invention, must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. The Examiner further states that if the microorganism(s) is not so obtainable or available, a deposit of the microorganism(s) in a recognized depository may satisfy the requirements of 35 U.S.C. § 112.

Applicants traverse the § 112, First Paragraph rejection and the depository requirement. As stated at page 3, lines 1-9 of the specification, the strains are "non-genetically modified," i.e., the strains are wild-type strains. At page 4, line 28 to page 5, line 18, Applicants disclose "*Bacillus sphaericus* (*B.s.*) is a rod-shaped, aerobic, spore-forming bacterium found commonly in soil and other substrates (emphasis added)." Thus, the Bacillus strains of the present invention are wild-type, isolated and biologically pure strains as available to the public under certain trademarks, i.e., VETROBAC, VECTOLEX and SPERIMOS. All are commercial formulations available from Valent BioSciences Corp.

Thus, the *Bacillus* strains, individually, are readily obtainable and available to the public. Accordingly, Applicants respectfully request withdrawal of the rejection of claims 23-34 under 35 U.S.C. §112, first paragraph.

Rejection of Claims 23-26 under 35 U.S.C. § 112, Second Paragraph

Claims 24-26 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Specifically, the Examiner states that claims 24-26 are rendered vague and indefinite by the term "non-genetically modified" because this term, in and of itself, does not adequately delineate its metes and bounds. The Examiner questions whether the term refers to all changes that occur in the bacterial genome, or only those that are induced by a certain agent or natural selection or recombinant-DNA technologies.

Applicants have amended the claims to use the well-accepted term "wild-type" instead. Applicants submit that the substituted terminology equates to "non-genetically modified" and is commonly used in the art. As defined elsewhere and by Lodish et al., Molecular Cell Biology, Fourth Edition (1999) at page 254, wild-type organisms are those that are non-mutants, normal organisms found in nature.

Applicants also assert that the term "non-genetically modified" may be interpreted with its broadest available definition. As stated by the Examiner at page 7 of the Office Action, the term may be defined to include both genomic and recombinant modifications. Applicants' use of this term and its substitute includes both genomic and recombinant modifications as interpreted by the Examiner.

Accordingly, Applicants request withdrawal of the rejection of claims 24-26 under 35 U.S.C. § 112, second paragraph in view of this amendment. If the Examiner finds the above language objectionable, Applicants request further suggestions in amending the claims regarding this issue.

Rejection of Claims 23-34 under 35 U.S.C. § 103

Claims 23-34 are rejected under 35 U.S.C. § 103 (a) as obvious over Rheaume *et al.*, USPN 5,560,909) in view of Meadows *et al.*, USPN 5,501,852. Applicants respectfully traverse this rejection.

Specifically, the Examiner states that Rheaume *et al.* disclose "an ingestable bioinsecticidal composition" comprising *Bacillus sphaericus* and/or *Bacillus thuringiensis, var. israelensis* along with ultraviolet light stabilizer. The Examiner points to Rheaume *et al.* at column 14, lines 43-49 and at column 15, lines 22-31, for support.

Claim 23, the only independent claim under consideration, calls for a composition comprising a combination of an isolated, biologically pure strain of *Bacillus thuringiensis* subspecies *israelensis* and an isolated, biologically pure strain of *Bacillus sphaericus* (emphasis added). As pointed out in Applicants' disclosure, Applicants have unexpectedly discovered the combination of both of the claimed strains to be effective in controlling Dipteran larvae and inhibiting larvicidal resistance to known pesticides. Currently in the art, new biopesticides are continually searched for because of the build-up of pesticidal resistance (See page 2, lines 4-7 of the Specification for instance). Although individually, biopesticides are commonly used, Applicants do not know of any teachings of the combination of the two strains as claimed, i.e., an isolated, biologically pure strain of *Bacillus thuringiensis* subspecies *israelensis* and an isolated, biologically pure strain of *Bacillus sphaericus*.

The Examiner has cited claims 1 and 9 of Rheaume *et al.* (column 14, lines 43-49 and column 15, lines 22-31). Claim 1 of Rheaume *et al.* specifically calls for "An ingestible biological insecticidal composition comprising an insecticidally effective amount of an ingestible biological insecticide selected from the group consisting of DNA viruses, RNA viruses, bacteria of the genus Bacillus and the insecticidally active products of such bacteria trapped by a precipitated charged polymer, said composition further comprising an ultraviolet light stabilzer..." (emphasis added). Claim 9 specifically calls for the composition as claimed wherein the bacteria is selected from the group consisting of *Bacillus*

thuringiensis, Bacillus sphaericus, Bacillus popilliae, Bacillus cereus, Bacillus lentimorbus and Bacillus fribourgensis (emphasis added). The claims use a Markush Grouping which means "one selected from the group of." Nowhere is it suggested in Rheaume *et al.*'s claim language that the claimed composition comprises two or more *Bacillus* strains, nor more specifically an isolated, biologically pure strain of *Bacillus thuringiensis* subspecies *israelensis* and an isolated, biologically pure strain of *Bacillus sphaericus* as claimed by Applicants.

Applicants have carefully reviewed the disclosure of Rheaume *et al.* in detail. Rheaume *et al.* suggest a composition comprising only one Bacillus strain in combination with other insecticidal compositions (such as additives and polymers), and does not include two or more *Bacillus* strains. Rheaume *et al.* only list several *Bacillus* strains as examples of strains to be chosen from that list. At column 7, lines 39-44 of Rheaume *et al.*, it is stated "It is also contemplated that the insecticidal compositions of the present invention can be mixed with other insecticidal compositions including nonentrapped ingestible biological insecticides in order to achieve an initial high level of insecticidal activity which is followed by a sustained level of activity due to the entrapped materials." Rheaume *et al.*'s objective is to use pesticides entrapped by charged polymers in order to increase water flotation ability as compared to unencapsulated or unentrapped insecticides. See abstract and column 2, lines 21-29 of Rheaume et al. for example. Nowhere in their disclosure is it of concern to decrease larvicidal resistance and therefore there is not a need for using two or more Bacillus strains.

The Examiner has cited Meadows *et al.* for their teaching spray drying the slurries containing both strains. Meadows *et al.* disclose only using the strain of *Bacillus thuringiensis* designated as M200 deposited under accession number NCIMB 40385. It is disclosed at column 5, lines 1-6 that other entomocidal compositions may be included with the disclosed strain of *Bacillus thuringiensis* designated as M200 deposited under accession number NCIMB 40385, such as a liquid adjuvant or a surfactant. Furthermore, the strain disclosed by Meadows *et al.* is not a non-genetically modified strain or a wild-type strain. Nowhere is it

disclosed or taught by Meadows *et al.* to combine two or more *Bacillus* strains, and more specifically an isolated, biologically pure strain of *Bacillus thuringiensis* subspecies *israelensis* and an isolated, biologically pure strain of *Bacillus sphaericus* as claimed by Applicants. Thus, Meadows *et al.* do not correct the deficiencies of Rheaume *et al.*

The Examiner not only suggests that the combination of both claimed strains in a slurry is obvious but also that the proportions of different components or ratios is deemed merely a matter of judicious selection and routine optimization, which is within the purview of the skilled artisan. Applicants respectfully traverse this rejection.

There have been no reports of prior art on how the fermentation slurries could be combined at various ratios or the preservation of activity on production scale and spray drying under optimal conditions so as to not only recover theoretical biopotencies but also result in significantly and synergistically increased biopotency. These were Applicants' unexpected, significant, and surprising observations. By combining the fermentation concentrates of *Bacillus thuringiensis subsp. israelensis and Bacillus sphaericus* after concentrating to certain solids level, preserving their biological activity and spray drying the mixture at optimum conditions, a single particle delivers toxins and spores of both *Bacillus thuringiensis subsp. israelensis and Bacillus sphaericus.* In other words, the mosquito larvae when ingesting a particle, gets a bite of both toxins resulting in enhanced mortality. This is a very unique and novel method of delivering two microbial Larvicides.

Fermentation of *Bacillus thuringiensis subsp. israelensis and Bacillus sphaericus* is very complex with varying requirements for media, growth conditions, cycle time, and recovery method. Applicants have shown that they can produce the microbials at commercially viable biopotency, preserve the activity and effectively recover the bioactivity by optimal spray drying. The spray-dried component is no longer a physical mixture as toxins from both *Bacillus thuringiensis subsp. israelensis and Bacillus sphaericus* are imbedded in a single particle. Thus, there is no significant opportunity for the larvae to preferentially

ingest one particle over the other. Otherwise, when a physical mixture is applied in aquatic habitats, both actives may not have similar distribution in the field and the larvae may not get to ingest both *Bacillus thuringiensis subsp. israelensis (Bti)* and *Bacillus sphaericus (Bs).*

By combining the biologicals in a concentrated slurry phase at desired ratios, spray drying such compositions, and applying them to the aquatic mosquito habitats, not only broad spectrum of mosquitocidal activity can be achieved, but one may also significantly reduce the potential for build up resistance specifically to *Bacillus sphaericus.* This method now has the potential to combat mosquito problems worldwide. Thus far, in countries like India and France where mosquitoes developed resistance to *B. spharicus*, no commercial applications of this microbial Larvicide are permitted. Rotation with *Bti* and/or physical mixtures are not always the preferred options. One has to market two products.

The mosquito population is very diverse and complex. Mosquito habitats are even more complex environments. Effective control by biological means is very much needed. Delivering two microbials in one package as described is the best way to combat this important problem. Further, no recombinant or genomic modifications is required, thus minimizing regulatory concerns.

Applicants can also combine or add to the biological slurry mixture other useful compositions such as a surfactant, UV protectant, a feeding stimulant, or protein stabilizers to further enhance the stability and effectiveness of the biologicals. Thus, more homogeneous formulation is obtained upon spray drying. No milling to fine powders is required.

The Rheaume *et al.* patent relates to methods of entrapment *of Bacillus thuringiensis var. israelensis* and other microbials in charged polymers. The invention of Rheaume et al. actually uses dried powder and does not start with the fermentation slurry concentrates in the encapsulation process. That invention reveals a method of precipitation and milling which can significantly reduce the potency. The methods of Rheaume *et al.* are also not economical at least on production scale. Rheaume *et al.* did not study spray drying microbial slurry

concentrates at certain solids level to achieve the desired potency. Their invention in no way relates to the present invention and thus the argument that the know-how is obvious is not valid. The main goal in Rheaume *et al.*'s invention was about improving the persistence in the environment by way of encapsulation with or without additives.

Meadows *et al.*'s patent relates to the biological control of Lepidopterous pests using *Bacillus thuringiensis*. This organism is used for control of terrestrial crop pests versus *Bacillus thuringiensis subsp. israelensis and Bacillus sphaericus* which are applied to aquatic pests. Their invention shows a method of fermentation and conversion to slurry concentrate by centrifugation or powder by spray drying. This is a method to produce the active ingredient. It does not relate in any way to the method of concentration to certain solids, such as mixing two biologicals, i.e., *Bacillus thuringiensis subsp. israelensis and Bacillus sphaericus* at certain desired proportions, the art of preserving the biological activity and spray drying at optimal conditions, and applying to aquatic systems for broad spectrum control of aquatic mosquito pests.

The Meadows *et al.* patent merely shows the art of physically combining *Bacillus thuringiensis* powder with inert ingredients to produce wettable powder, dust, or granule. This method also requires milling which is not conducive to biologicals. Again, these are physical mixtures and not integrated at the slurry phase or just prior to spray drying. Such methods are obvious to any one involved in the skill of formulating. The present invention is totally different and not obvious especially in the art of combining two biologicals, recovering and delivering for effective control of mosquito larvae as well as in the managing of resistance.

For the reasons stated above, Applicants respectfully submit that the disclosures of Rheaume *et al.* and Meadows *et al.*, individually or in combination, do not disclose nor teach the subject matter as claimed in claims 23-34. Examiner is respectfully requested to withdraw the art rejection.

CONCLUSION

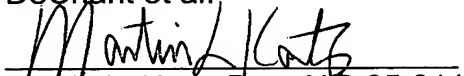
Applicants respectfully submit that the claims comply with the requirements of 35 U.S.C. Sections 101, 112, 102 and 103. Accordingly, a Notice of Allowance is believed in order and is respectfully requested.

Should the Examiner have any questions concerning the above, the Examiner is respectfully requested to contact the undersigned at the telephone number listed below. If the Examiner notes any further matters which the Examiner believes may be expedited by a telephone interview, the Examiner is requested to contact the undersigned.

If any fees are incurred as a result of the filing of this paper, authorization is given to charge Deposit Account Number 23-0785.

Respectfully submitted,

DeChant et al.



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